Ambulatory versus Home Blood Pressure Monitoring: Frequency and Determinants of Blood Pressure Difference and Diagnostic Disagreement

Short title: Ambulatory versus home blood pressure

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Conflicts of Interest: RM: Received BP monitoring equipment for research purposes from Omron and Lloyds Pharmacies. GS: Conducted validation studies of BP monitors of various manufacturers and advised manufacturers on device and software development. AJ, AK, AL, AN, CS, EA, TN: None.

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Abstract

Objectives: Out-of-office blood pressure (BP) evaluation assessed using ambulatory (ABP) or home (HBP) monitoring is currently recommended for hypertension diagnosis and management. This study evaluated the frequency and determinants of diagnostic disagreement between ABP and HBP measurements.

Methods: Cross-sectional data from 1,971 subjects (mean age 53.8±11.4 years, 52.6% males, 32% treated) from Greece, Finland and UK were analyzed. The diagnostic disagreement between HBP and daytime ABP was regarded as *certain* when (i) the two methods diagnosed a different BP phenotype, (ii) the absolute HBP-ABP difference was >10/5 mmHg (systolic/diastolic), and (iii) ABP and HBP had a >5 mmHg difference from the respective hypertension threshold.

Results: In 1,574 subjects (79.9%) there was agreement between HBP and daytime ABP in diagnosing hypertensive phenotypes (kappa 0.70). Of the remaining 397 subjects (20.1%) with diagnostic disagreement, 95 had *diagnostically uncertain* HBP-ABP differences and, therefore the disagreement was reduced to 15.3%. When cases with ABP and/or HBP differing ≤5 mmHg from the respective hypertension threshold were excluded, the *certain* disagreement between the two methods was reduced to 8.2%. Significant determinants of the HBP-ABP difference were age, gender, study center, body mass index, cardiovascular disease history, office hypertension and antihypertensive drug treatment. Antihypertensive drug treatment, alcohol consumption and office normotension independently increased the odds of diagnostic disagreement.

Conclusions: These data suggest that there is considerable diagnostic agreement between HBP and ABP, and that these methods are interchangeable for clinical decisions in most patients. However, considerable disagreement between the two methods occurs in an appreciable minority, most likely due to methodological and patient-related factors.

Keywords: agreement; decision making; diagnosis; masked hypertension; self-measurement; discordance; white-coat hypertension

Condensed abstract

The frequency and determinants of ambulatory and home BP difference and diagnostic disagreement were analyzed in 1,971 subjects from 3 European countries. Considerable home-ambulatory BP difference (>10/5 mmHg) was found in about half of the participants. However, there was diagnostic agreement in 80%, with certain disagreement in 8%. Age, gender, study center, obesity, cardiovascular disease, alcohol consumption, office BP and antihypertensive treatment determined the BP differences and diagnostic disagreement. Despite the close diagnostic agreement between home and ambulatory BP with these methods being interchangeable in most patients, considerable disagreement is not uncommon and is due to methodological and patient-related factors.

Abbreviations

ABP Ambulatory blood pressure

BP Blood pressure

HBP Home blood pressure

IQR Interquartile range

MH Masked hypertension in untreated or masked uncontrolled hypertension in treated subjects

NT Normotension in untreated or controlled hypertension in treated subjects

OBP Office blood pressure

OR Odds ratio

SH Sustained hypertension in untreated or uncontrolled hypertension in treated subjects

WCH White-coat hypertension in untreated or white-coat uncontrolled hypertension in treated subjects

INTRODUCTION

Out-of-office blood pressure (BP) monitoring, performed using 24-hour ambulatory BP (ABP) or self-home BP (HBP) monitoring, is currently recommended by several organizations as indispensable for the optimal diagnosis and management of hypertension [1-4]. Reasons for this include the much larger number of BP measurements available from ABP and HBP monitoring compared to conventional office BP (OBP) measurement, and the fact that they are taken in the usual environment of each individual, leading to closer association with outcome than OBP measurements [5-8]. Moreover, ABP and HBP monitoring identify the white-coat and masked hypertension phenomena, which are common among both untreated and treated subjects and often lead to misdiagnosis and mismanagement of hypertension [9-10]. Predictors of discordance between office and out-of-office BP measurements have been investigated in previous studies [11-15].

Although daytime ABP and HBP monitoring share several advantages and have major similarities and the same recommended threshold for hypertension, they can give dissimilar BP values leading to contradictory conclusions [1,2]. Thus, the diagnostic agreement between the two methods is considered fair to moderate. Current guidelines regard the two methods as interchangeable but also complementary, as they are inherently dissimilar in several major aspects (measurement environment, activity, posture, schedule, timing), influenced by different types of BP variability (short, medium and long-term) and therefore reflect different aspects of the BP profile and behaviour [1,2]. The reasons and factors related with diagnostic disagreement between ABP and HBP measurements remain uncertain.

The objectives of this study were to: (i) quantify the frequency of considerable differences between HBP and ABP measurements; (ii) assess the prevalence of diagnostic disagreement between the two methods; and (iii) identify major determinants of the HBP/ABP difference and disagreement.

METHODS

This retrospective analysis included data collected prospectively in the context of cross-sectional clinical studies of untreated or treated adults evaluated with OBP, HBP and ABP measurements using similar protocols according to current guidelines. All research protocols had been approved by local scientific/ethics committees and all participants had provided written informed consent for their participation.

Subjects

Ambulatory subjects aged ≥18 years on stable antihypertensive drug treatment for at least 4 weeks or untreated were recruited in 3 centers (Athens, Greece; Birmingham, UK; Turku, Finland). The Athens center included outpatients referred to a University hospital BP clinic. The Birmingham center included a primary care population of individuals known or not to be hypertensives. The Finnish center recruited three samples; the first (Finland-1) included untreated hypertensives referred to a hypertension research center for evaluation before treatment initiation and the other two (Finland-2 and -3) included random population samples. Exclusion criteria were severe cardiac, renal or other systemic diseases, sustained arrhythmia, pregnancy and evidence of secondary hypertension.

BP measurements

BP was measured in the office within 10 days (Birmingham), 2 weeks (Athens) or 3 weeks (Finland). HBP and ABP monitoring were performed within the abovementioned office visits in random order (ABP monitored before or after HBP monitoring). Eligible participants had the following minimum measurements available: OBP (≥1 visit and ≥2 readings), HBP (≥3 days and ≥12 readings) and ABP (≥14 daytime and ≥7 night-time readings).

Office BP measurement

At each office visit, two (Finland-1, Finland-2), three (Athens, Finland-3) or six (Birmingham) OBP measurements were taken in sitting position, after at least 5 minutes rest, using a standard mercury sphygmomanometer or validated automated upper arm-cuff devices (Microlife WatchBP Office or WatchBP Central [Microlife, Widnau, Switzerland], or BpTRU [BpTRU Medical Devices, Coquitlam, BC, Canada]) using cuff size appropriate to each individual's arm circumference, in 1-4 visits performed within 10-21 days. Measurements were performed at outpatient clinics by research physicians (Athens), research facilitators (Birmingham) or nurses (Birmingham, Finland-1-3). The first 2-3 readings of each visit were used and the average of readings of the first 1-3 visits (range 2-9 readings) was used in the analysis.

Home BP monitoring

Participants were instructed to take duplicate self-home BP measurements after a 2-5-minute sitting rest and with 1-minute interval between measurements using validated electronic upper arm-cuff devices (Omron HEM-705CP, HEM 705C, HEM 705, HEM-705IT [Omron Healthcare UK Ltd., Milton Keynes, UK], or Microlife WatchBP Home, Microlife WatchBP HomeN [Microlife, Widnau, Switzerland]) using cuff size appropriate to each individual's

arm circumference, in the morning (6-12 am, before drug intake if treated) and evening (6-12 pm) for 7 days within 1-2 weeks. Subjects were instructed in the conditions of HBP measurements and the use of the devices. All HBP monitors, except those used in Finland-1 and Finland-2 cohorts, had in-built automated memory capacity and BP data were downloaded through a computer link. Subjects with at least 12 valid HBP readings were included. The average value of all 12-28 HBP readings collected in 3-7 days was calculated for each participant.

Ambulatory BP monitoring

ABP was monitored on a routine workday using validated oscillometric devices (Microlife WatchBP O3, Microlife, Widnau, Switzerland; Spacelabs 90207 or 90217 or 90217-1Q, Spacelabs Medical, Issaquah, WA) or automated auscultatory devices (Accutracker II, Suntech Medical Instruments, Raleigh, North Carolina, USA) with measurements scheduled at 15-30 minutes intervals during daytime and 20-60 minutes during night-time. Day and night periods were defined according to the individual patients' diaries, apart from the Birmingham study that used fixed night-time period (11 pm-7 am). Average 24-hour and daytime ABP was calculated.

Definitions

BP differences between methods

BP differences by >10/5 mmHg (systolic/diastolic) larger than the expected average difference (which is 0/0 mmHg for HBP versus daytime ABP and +5/+5 mmHg for HBP versus 24-hour ABP) were defined as '*diagnostically certain*' and smaller ones (ie. HBP

versus daytime ABP difference ranging from -10/-5, systolic diastolic, to +10/+5 mmHg or HBP versus 24-hour ABP difference from -5/0 to +15/+10 mmHg) as '*diagnostically uncertain*' on the basis of the likely effect on clinical decision making.

BP phenotypes

The BP thresholds for hypertension diagnosis were 140/90 mmHg (systolic/diastolic) for OBP, 135/85 mmHg for HBP and daytime ABP, and 130/80 mmHg for 24-hour ABP [10]. White-coat hypertension (in untreated or white-coat uncontrolled hypertension in treated) (WCH) was defined as elevated systolic and/or diastolic OBP and normal systolic and diastolic HBP (or ABP). Masked hypertension (in untreated or masked uncontrolled hypertension in treated) (MH) were defined as elevated systolic and/or diastolic HBP (or ABP) and normal systolic and diastolic OBP. Sustained hypertension (in untreated or uncontrolled hypertension in treated) (SH) was defined as elevated systolic and/or diastolic OBP and HBP (or ABP) and normotension (in untreated or controlled hypertension in treated) (NT) as normal systolic and diastolic OBP and HBP (or ABP).

Diagnostic disagreement between methods

The diagnostic disagreement between HBP and ABP was regarded as *certain* when (i) the two methods diagnosed a different BP phenotype (see above), (ii) there was a '*diagnostically certain*' HBP-ABP difference (see above), and (iii) ABP and HBP had a >5 mmHg difference (systolic and/or diastolic) from the respective hypertension threshold.

Statistical analysis

The normality of variables was checked using the Kolmogorov-Smirnov test. Comparison of OBP, HBP and ABP values in the same subjects was performed with student's paired t-tests with Bonferroni correction applied when required. Continuous variables were compared among groups or study centers with one-way analysis of variance (ANOVA) or Kruskal-Wallis test as appropriate. Chi-squared test was used to compare categorical variables. Modified Bland-Altman scatterplots were used to investigate the agreement between HBP and ABP measurements. Proportions of *diagnostically certain* and *uncertain* BP differences were also calculated. The diagnostic agreement between ABP and HBP in detecting hypertension phenotypes was assessed using kappa statistics. Associations between quantitative variables were assessed with bivariate correlation analyses, computing either Pearson's or Spearman's correlation coefficients as appropriate. Predictors of diagnostic disagreement and determinants of the HBP-ABP difference were assessed using logistic regression analysis and multivariate linear regression analysis, respectively. Independent variables were age, gender, ethnicity, body mass index, cardiovascular disease, diabetes mellitus, hypercholesterolemia, smoking status, alcohol consumption, OBP level, antihypertensive drug treatment status, study center (included as an independent categorical variable [5 levels: Athens, Birmingham, Finland-1, Finland-2, Finland-3] with dummy coding) and number of HBP readings. Additional sensitivity analyses were performed in untreated versus treated subjects, participants with low versus elevated OBP and in age subgroups ≤30, 30-60 and ≥60 years. The IBM SPSS Statistics 21 (SPSS Inc., Chicago, IL, USA) software was used. Results are expressed as means ±standard deviation (SD) or medians with interquartile range (IQR), as appropriate. A two-sided probability value of $p<0.05$ was considered statistically significant.

RESULTS

Data from 2,383 subjects were collected from the 5 datasets of whom 1,971 had complete and valid BP data for all the three BP monitoring methods and were included in the analysis. Participants' characteristics are presented in **Table 1.** Mean age was 53.8±11.4 years, 52.6% were men and 32% were treated for hypertension. Comparison of participants' characteristics among the 5 cohorts is provided in **Suppl. Table 1** (Supplemental Digital Content 1). The median number of OBP readings was 6 (IQR: 6-8), of HBP readings 26 (IQR:24-28), daytime ABP 43 (IQR: 31-56) and 24-hour ABP readings 66 (IQR:41-75). Average BP with each method is shown in **Table 2.**

OBP was correlated with HBP (r 0.69/0.77, systolic/diastolic, $p<0.001$), daytime ABP (r 0.64/0.74, $p<0.001$) and 24-hour ABP (r 0.63/0.72, $p<0.001$). HBP was correlated with daytime ABP (r 0.73/0.81, $p<0.001$) and 24-hour ABP (r 0.74/0.82, $p<0.001$).

OBP was higher than HBP (by 1.9±13.3/2.4±7.7 mmHg, systolic/diastolic, both $p<0.001$), daytime ABP (0.5±14.5/2.3±8.0 mmHg; p=NS/<0.001) and 24-hour ABP (5.2±14.7/6.2±8.2 mmHg; both $p<0.001$). HBP was higher than 24-hour ABP by 3.3±10.5/3.8±6.0 mmHg and slightly lower than systolic daytime ABP by 1.4±10.8 (all $p<0.001$, **Table 2**). There was no difference between diastolic HBP and daytime ABP (difference -0.01±6.4 mmHg; p=NS).

Modified Bland-Altman scatterplots for HBP-daytime ABP difference are shown in **Figure 1**. Diastolic BP showed less dispersion from the average difference than systolic. Bland-Altman

scatterplots by center showed considerable heterogeneity, with the Finnish cohorts 1 and 2 exhibiting larger BP differences **(Suppl. Figures 1 and 2**, Supplemental Digital Content 1).

The distribution of HBP versus daytime ABP differences is shown in **Figure 2.** For systolic/diastolic BP 66.6%/58.7% of the participants had *diagnostically uncertain* differences (within 10/5 mmHg). A percentage of 46.5% of the participants had *diagnostically uncertain* systolic and/or diastolic HBP-ABP differences (combined systolic/diastolic BP differences within 10/5 mmHg). When 24-hour ABP instead of daytime was used, the proportion of *diagnostically uncertain* systolic/diastolic BP differences from HBP were 68%/59.7% (49.2% when both systolic and diastolic BP were considered).

Using the hypertension thresholds for each method, subjects were classified as normotensives, white-coat, masked and sustained hypertensives **(Table 1; Suppl. Figure 3**, Supplemental Digital Content 1). There was diagnostic agreement between ABP and HBP in detecting hypertension phenotypes in 1,574 subjects (79.9%; kappa statistic 0.70 for daytime and 0.71 for 24-hour ABP) (**Suppl. Table 2,** Supplemental Digital Content 1). Of the remaining 397 subjects (20.1%) with diagnostic disagreement, in 95 the HBP-ABP difference was '*diagnostically uncertain*' and, therefore, the disagreement was reduced to 15.3% **(Suppl. Figure 4A and 5**, Supplemental Digital Content 1). When a 5-mmHg grey zone of diagnostic uncertainty was applied around the HBP and ABP thresholds for hypertension (cases with HBP and/or ABP difference ≤5 mmHg from the respective threshold excluded as diagnostically uncertain) the disagreement was further decreased to 8.2% **(Figure 3; Suppl. Figure 4A**, Supplemental Digital Content 1).

The same analysis performed separately in treated and untreated subjects **(Suppl. Figure 4B,** Supplemental Digital Content 1) showed that untreated subjects had higher levels of agreement (83.1%, kappa 0.74) versus treated (72.9%, kappa 0.62; p<0.001) and less disagreement with *diagnostically certain* BP differences (12.8% versus 20.6%, respectively; p<0.001). Furthermore, better diagnostic agreement between HBP and daytime ABP was observed in participants with office hypertension (systolic and/or diastolic, N=990) compared with those with office normotension (N=981) (83.3% versus 76.4%, p<0.001, with kappa 0.42 versus 0.46, respectively; **Suppl. Table 3**, Supplemental Digital Content 1). By removing cases with *diagnostically uncertain* differences, the disagreement was found to be lower in subjects with office hypertension than with office normotension (13.4% versus 17.2%, respectively; p=0.02). After discarding cases within a 5-mmHg grey zone of diagnostic uncertainty around the threshold for HBP and ABP hypertension for the participants with diagnostic disagreement, the *certain* disagreement was again lower in untreated than in treated participants (6.2% versus 12.5%, p<0.001; **Suppl. Figure 4B**, Supplemental Digital Content 1) but didn't differ between subjects with office hypertension and those with office normotension (7.4% versus 9.1%, respectively; p=0.19; **Suppl. Table 3; Suppl. Figure 6,** Supplemental Digital Content 1). Secondary analyses using 24-hour ABP instead of daytime ABP gave similar results with the main analysis (data not shown).

In linear regression analysis **(Table 3)** older age, higher body mass index and office hypertension consistently determined larger HBP - daytime ABP differences, and center (cohort) was the strongest determinant (all p<0.05). Additional positive determinants were cardiovascular disease history for systolic BP difference and male gender and antihypertensive treatment for diastolic BP difference (all p<0.05). Linear regression analysis

for determinants of HBP - 24-hour (instead of daytime) ABP difference gave similar results. These findings are supported by subgroup analyses **(Suppl. Table 4,** Supplemental Digital Content 1). When regression sensitivity analyses were performed by excluding one cohort at a time (**Suppl. Tables 5-6**, Supplemental Digital Content 1), similar results were obtained as with all cohorts analyzed together, with occasional differentiation mainly in the role of gender, antihypertensive treatment and cardiovascular disease history.

In logistic regression analysis, antihypertensive drug treatment (odds ratio [OR] 1.48, $p<0.05$), alcohol intake (OR 1.02 per 10 gr increase in weekly alcohol consumption, $p<0.05$) and low OBP levels (OR 1.84, $p<0.001$) independently increased the odds of diagnostic disagreement between HBP and daytime ABP.

DISCUSSION

These cross-sectional data based on 1,971 treated or untreated individuals from 5 centers in 3 European countries who underwent OBP, HBP and ABP measurements using similar protocols according to current guidelines showed that: (i) average systolic HBP was slightly lower than daytime ABP (by 1.4 mmHg), with no difference in diastolic BP, but higher than 24-hour ABP (by 3.3/3.8 mmHg, systolic/diastolic); (ii) the HBP-ABP differences were *diagnostically certain* in 33.4% of the participants for systolic (>10 mmHg) and 41.3% for diastolic BP (>5 mmHg); (iii) there was good diagnostic agreement between HBP and ABP in detecting hypertension phenotypes (80%, kappa 0.70); (iv) of the participants with diagnostic disagreement, 24% had *diagnostically uncertain* BP differences between the two methods (≤10/5 mmHg systolic/diastolic) reducing the disagreement to 15.3%; (v) by

applying a 5-mmHg grey zone of diagnostic uncertainty around the diagnostic thresholds for HBP and ABP hypertension the *certain* diagnostic disagreement was limited to 8.2%; (vi) determinants of a larger HBP-ABP difference were older age, gender, study center, higher body mass index, cardiovascular disease history, office hypertension and antihypertensive drug treatment and predictors of diagnostic disagreement were antihypertensive drug treatment, alcohol consumption and office normotension.

Because of the inherent methodological differences between ABP and HBP, these data showing 53.5% of subjects having >10/5 mmHg systolic/diastolic HBP-ABP differences, here defined as *diagnostically certain,* are not surprising, yet indeed alarming for clinical practice. The practical question, however, is whether these measurements with sizeable BP differences, result in different diagnoses and treatment decisions. Thus, the diagnostic disagreement between HBP and ABP rather the BP difference is highly relevant for clinical practice.

In the present analysis we defined diagnostic disagreement between HBP and ABP as *certain* when there was considerable difference between them (>10/5 mmHg, systolic/diastolic) and both of them differed considerably (>5 mmHg) from the respective hypertension threshold **(Suppl. Figure 7**, Supplemental Digital Content 1). The diagnostic disagreement is based on two BP thresholds, and when BP is close to the threshold this is not clinically relevant for the practicing physician. Furthermore, diagnostic disagreement in cases with HBP or ABP being close to the diagnostic threshold (within 5 mmHg) are here considered as uncertain due to the imperfect reproducibility of both methods **(Suppl. Figure 7,** Supplemental Digital Content 1) [16].

Despite the important methodological differences between HBP and ABP, and the high frequency of large BP differences between them demonstrated in this study, the 80% diagnostic agreement between HBP and ABP in identifying hypertensive phenotypes is very reassuring **(Suppl. Table 2,** Supplemental Digital Content 1). This finding confirms previous studies reporting considerable diagnostic agreement between the two methods ranging from 70 to 90% [18-21]. Moreover, there are arguments supporting even higher agreement. First, when cases with small BP disagreement (≤10/5 mmHg; systolic/diastolic) are excluded the diagnostic disagreement is reduced to 15.3%. Second, this disagreement should be adjusted for the imperfect reproducibility of both methods (disagreement between repeated HBP or ABP monitoring sessions), which is not negligible [16,17]. Thus, when a 5-mmHg grey zone of diagnostic uncertainty was applied around the diagnostic thresholds for HBP and ABP hypertension, the diagnostic disagreement was further reduced to 8.2% (*certain* disagreement). Third, the diagnostic disagreement is expected to be larger in subjects with BP levels close to the diagnostic thresholds, as in the present study **(Table 2)**, than in subjects with very high or very low BP.

Another challenging finding of this study is that the HBP/ABP agreement was greater in untreated than in treated subjects. These data suggest that, by taking ABP monitoring as reference, HBP monitoring appears to be a reliable alternative to ABP for initial diagnosis of hypertension, at least as much (if not better) as for the management of treated hypertension.

The primary analysis of this study was based on daytime ABP. This approach was chosen because (i) some guidelines such as those by the UK NICE [3] and the US 2017 [2]

recommend daytime ABP for decision making; (ii) HBP and daytime ABP involve only daytime (awake) measurements; (iii) the same BP threshold is recommended for both. However, 24-hour ABP should be preferred for two reasons. First, night-time ABP is regarded as the most important aspect of the 24-hour profile in terms of prognosis. Second, it doesn't seem sensible to discard additional data readily provided by 24-hour ABP monitoring [9, 22]. Although, including night-time ABP brings into the ABP/HBP comparison another major source of differentiation (awake HBP versus awake and asleep ABP), the overall results for all aspects of the ABP/HBP comparison were impressively similar with 24-hour and daytime ABP.

A key determinant of the HBP-ABP difference was the cohort factor. This was expected as there were differences in the HBP-ABP comparison between cohorts, with the Finnish-1 and 2 having much lower HBP than daytime ABP **(Suppl. Figure 1**, Supplemental Digital Content 1). This deviation might be attributed to different participant characteristics, as the Finland-1 cohort included exclusively untreated subjects with higher OBP and cardiovascular disease. Furthermore, Finland-1 and 2 data were collected in the 1990s using the same ABP (automated auscultatory Accutracker II) and HBP monitors (semi-automatic oscillometric with manual cuff inflation) [23], compared to fully automated oscillometric devices in the other cohorts. Sensitivity analyses performed after excluding one cohort at a time showed only occasional differences compared to all-cohorts analysis, which might be chance phenomena due to multiple analyses.

Increasing age was a significant determinant of HBP being higher than ABP. This finding is supported by previous data in untreated individuals, which also showed younger adults to

have lower HBP than daytime ABP levels, whereas those aged >60 years had the reverse [24]. Older subjects have less physical activity, no job strain after retirement, and often orthostatic hypotension, all of which reduce daytime ABP [25]. Moreover, self-measurement may be more difficult and stressful in the elderly, resulting into higher HBP values.

Antihypertensive drug treatment might also result in higher HBP than ABP, given that morning HBP measurements (50%) are obtained before drug intake (trough), whereas ABP also includes BP readings at peak effect. In addition, in treated hypertensives ABP is more likely to identify orthostatic hypotension than HBP, as only the former provides readings in standing posture.

Other factors that appeared to exaggerate the HBP-ABP difference were obesity, cardiovascular disease history and the presence of office hypertension. These findings might be due to less intense physical activity of individuals with higher body mass index or cardiovascular comorbidity and by the anxiety induced in some patients due to the high OBP diagnosis resulting into higher self-measured BP than automatically-taken ABP.

The most clinically relevant issue examined in this study is the predictors of diagnostic disagreement between HBP and ABP. The data showed that antihypertensive treatment and office normotension led to a greater probability of diagnostic discordance. Potential mechanisms were discussed above. Another interesting finding is that alcohol consumption increased the probability of disagreement between methods. This is in line with previous reports and might be due to the temporal nature of relationship between alcohol intake and BP elevation (early BP lowering effect in the hours after exposure and a later BP rising effect

in the following day) that affects the BP monitoring methods in a different manner due to different timing and conditions of measurements [26-28].

The main advantage of this study is the direct comparison of HBP and ABP levels in a large sample assessed with similar BP monitoring protocols and in accordance with current guidelines. Limitations are the cross-sectional design and the differences among cohorts in participants' characteristics, as well as several methodological and technical differences. Furthermore, the use of wide-fixed (and not narrow-fixed) definition of night-time period in the Birmingham study may have led to overestimation of nocturnal BP compared to diary-based approach used in the remaining studies.

Conclusions

HBP and ABP measured in standardized conditions according to recommended protocols provide similar diagnostic conclusions in the vast majority of untreated and treated hypertensives. However, there is diagnostic disagreement in a considerable number of patients, which can be attributed to intrinsic characteristics of the methods, differences in the individuals' characteristics and behavior, as well as technical differences. Thus, these methods are not fully interchangeable, but often provide complementary information.

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Conflicts of Interest-

RM: Received BP monitoring equipment for research purposes from Omron and Lloyds Pharmacies. GS: Conducted validation studies of BP monitors of various manufacturers and advised manufacturers on device and software development. AJ, AK, AL, AN, CS, EA, TN: None.

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Table 1. Participants' characteristics.

Characteristics	
N	1,971
Males (%)	1,037 (52.6)
Ethnicity (%)	
- Caucasian	1,716 (87.1)
- African Caribbean	138 (8.0)
- South Asian	117 (5.9)
Age (range; years)	53.8±11.4 (18-86)
Body mass index (kg/m^2)	28.4±5.3
Waist circumference (cm)	95.3±14.5
Current smoking (%)	395 (21.4)
Alcohol consumption (gr/week)	53.4±94.3
Antihypertensive treatment (%)	631 (32.0)
Cardiovascular disease (%)	123 (6.6)
Diabetes mellitus (%)	145 (7.8)
Hypercholesterolemia (%)	958 (51.2)
Hypertension (%)	
- Office BP	990 (50.2)
- Home BP	1,140 (57.8)
- Daytime ambulatory BP	1,123 (57.0)
NT/WCH/MH/SH (%)	
- Home BP	34.0/8.1/15.7/42.1
- 24-hour Ambulatory BP	32.2/9.0/17.6/41.2
- Daytime Ambulatory BP	33.6/9.4/16.1/40.8

BP, blood pressure; NT, normotension (in untreated or controlled hypertension in treated); WCH, white-coat hypertension (in untreated or white-coat uncontrolled hypertension in treated); MH, masked hypertension (in untreated and masked uncontrolled hypertension in treated); SH, sustained hypertension (in untreated or uncontrolled hypertension in treated).

Missing values: smoking 128, cardiovascular disease 95, diabetes 102, hypercholesterolemia 101.

Table 2. Office, home and ambulatory blood pressure measurements (mean±SD, mmHg).

Blood pressure measurement		**Systolic**	**Diastolic**
Office	1-3 visits	135.7±18.2	86.0±11.8
Home	3-7 days	133.8±15.0	83.6±10.3
Ambulatory	24-hour	130.5±14.3	79.8±9.8
	Daytime	135.2±14.8	83.7±10.5
	Night-time	118.0±15.2	70.1±9.9

Table 3. Linear regression models for determinants of the difference between home and daytime ambulatory blood pressure (BP).

	Systolic	**Diastolic**
R^2	0.26	0.12
Determinants	**β coefficients**	
Age (years)	0.20*	0.09*
Female gender	0.03	-0.65*
Antihypertensive treatment	1.04	0.82*
Ethnicity (vs Caucasians)		
- African Caribbean	1.01	0.62
- South Asians	1.58	0.86
Center (vs Birmingham)		
- Finland-1	-8.07*	1.07
- Finland-2	-5.49*	0.31
- Finland-3	-1.94	-1.28
- Athens	1.29	-1.75*
Body mass index (kg/m^2)	0.21*	0.22*
Cardiovascular disease	2.09*	1.21
Diabetes	0.78	0.43
Hypercholesterolemia	-0.04	-0.02
Smoking	0.24	-0.04
Alcohol (per 10 gr/week)	-0.02	-0.01
Office hypertension	1.32*	1.05*
Number of home BP readings	-0.08	-0.05

Results adjusted for age, gender, body mass index, ethnicity, cardiovascular disease, diabetes, hypercholesterolemia, smoking status, alcohol

consumption, office BP level, antihypertensive drug treatment status, study center and number of home BP readings; *, $p<0.05$).

Legend to Figure 1.

Scatterplot of differences between home and daytime ambulatory blood pressure (BP) difference (shaded area represents *diagnostically uncertain* differences (≤10/5 mmHg; systolic/diastolic).

Legend to Figure 2.

Distribution of differences between home and daytime ambulatory blood pressure (BP; shaded area represents *diagnostically uncertain* differences ≤10/5 mmHg).

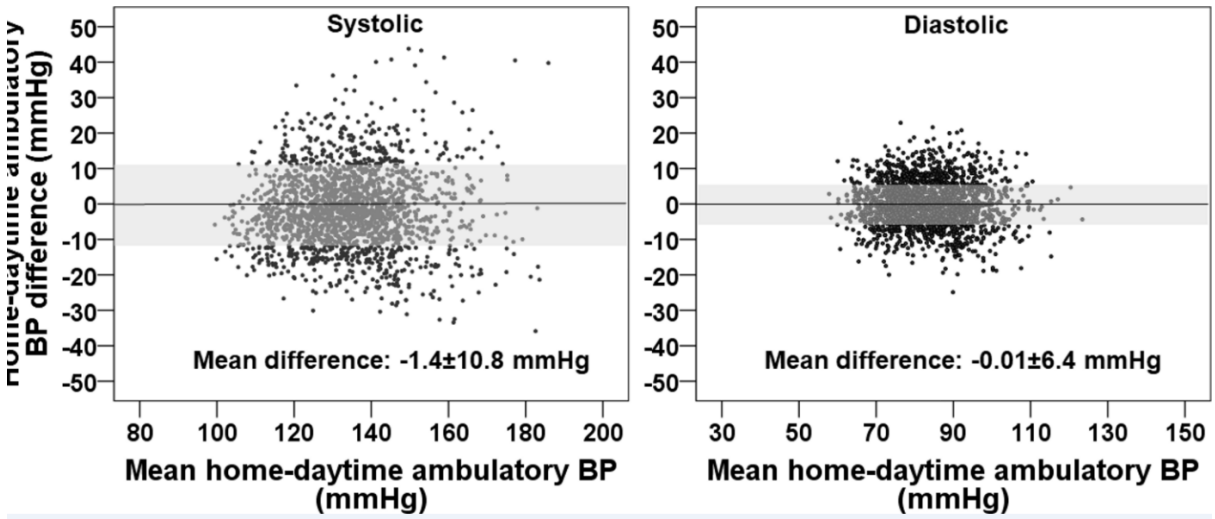
Legend to Figure 3.

Disagreement between daytime ambulatory (ABP) and home (HBP) blood pressure monitoring in the diagnosis of hypertension phenotypes. Grey-shaded area represents a 5-mmHg zone of uncertain diagnosis which is close to the diagnostic thresholds.

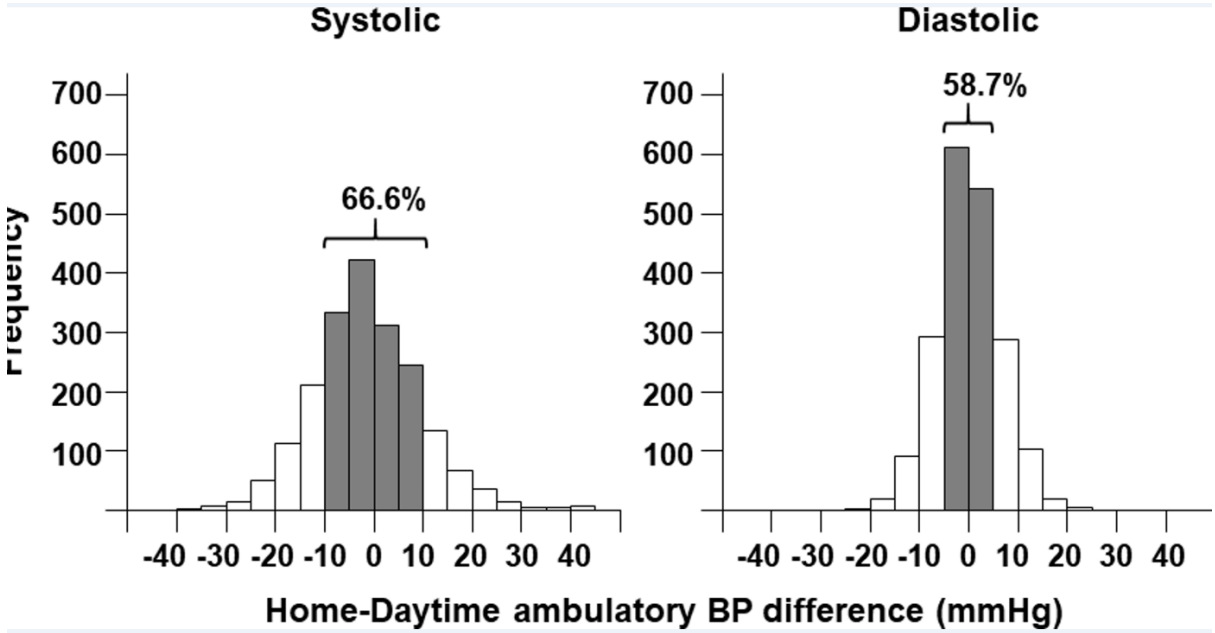
List of Supplemental Digital Content

- Supplemental Digital Content 1 Suppl. figures 1-7 and suppl. tables 1-6. pdf

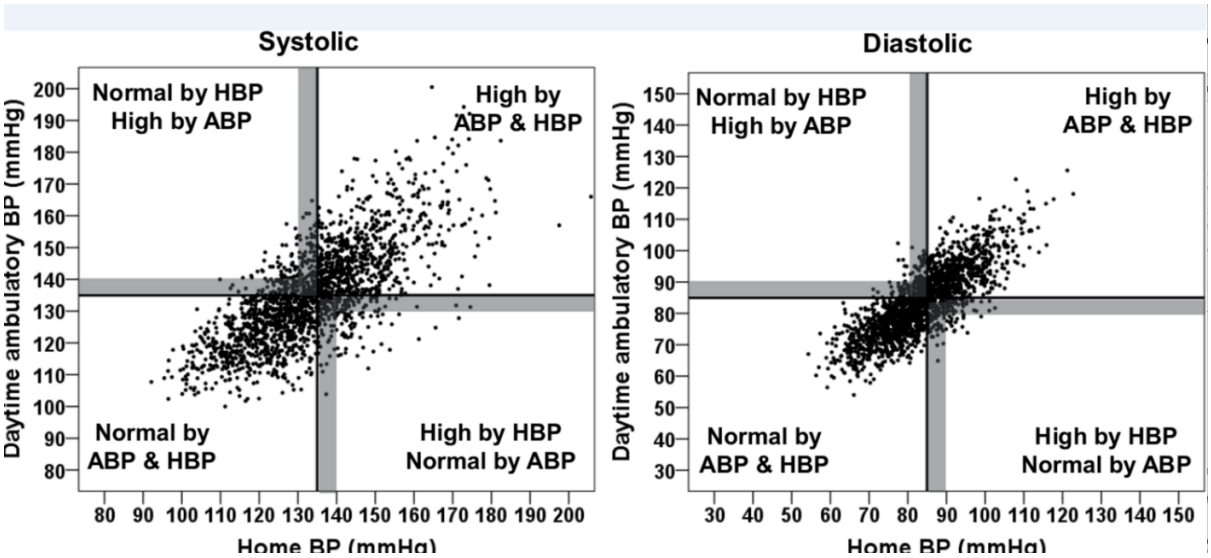
- Figure 1:



- Figure 2:



- Figure 3:



Supplemental Digital Content (SDC)

Ambulatory versus Home Blood Pressure Monitoring: Frequency and Determinants of Blood Pressure Difference and Diagnostic Disagreement

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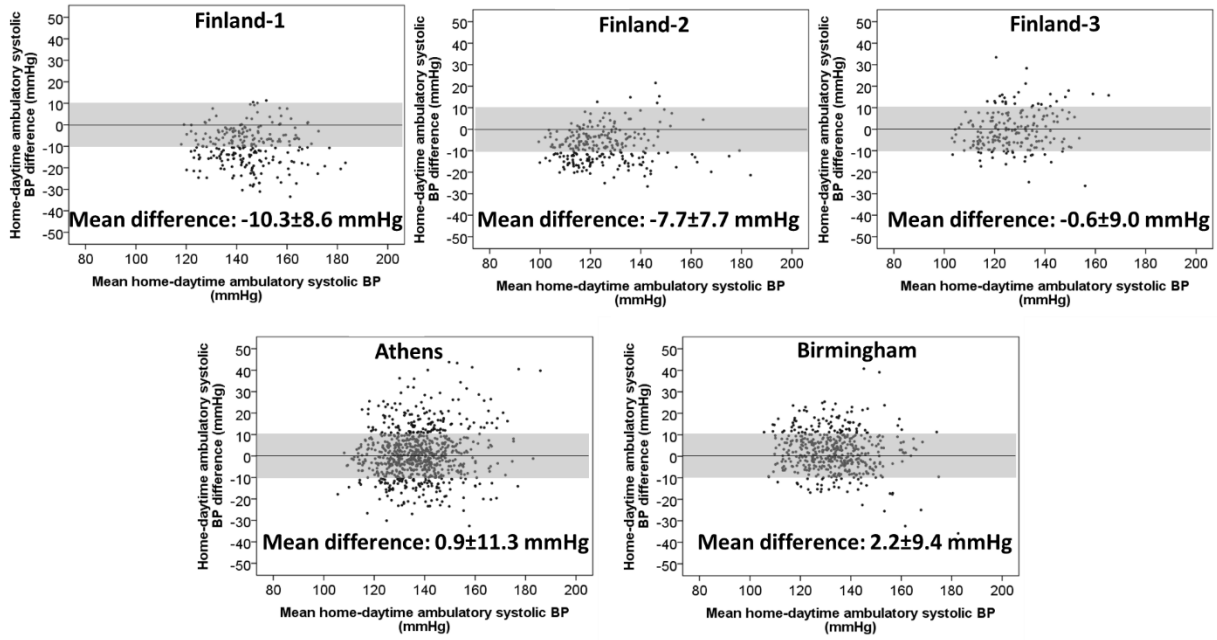
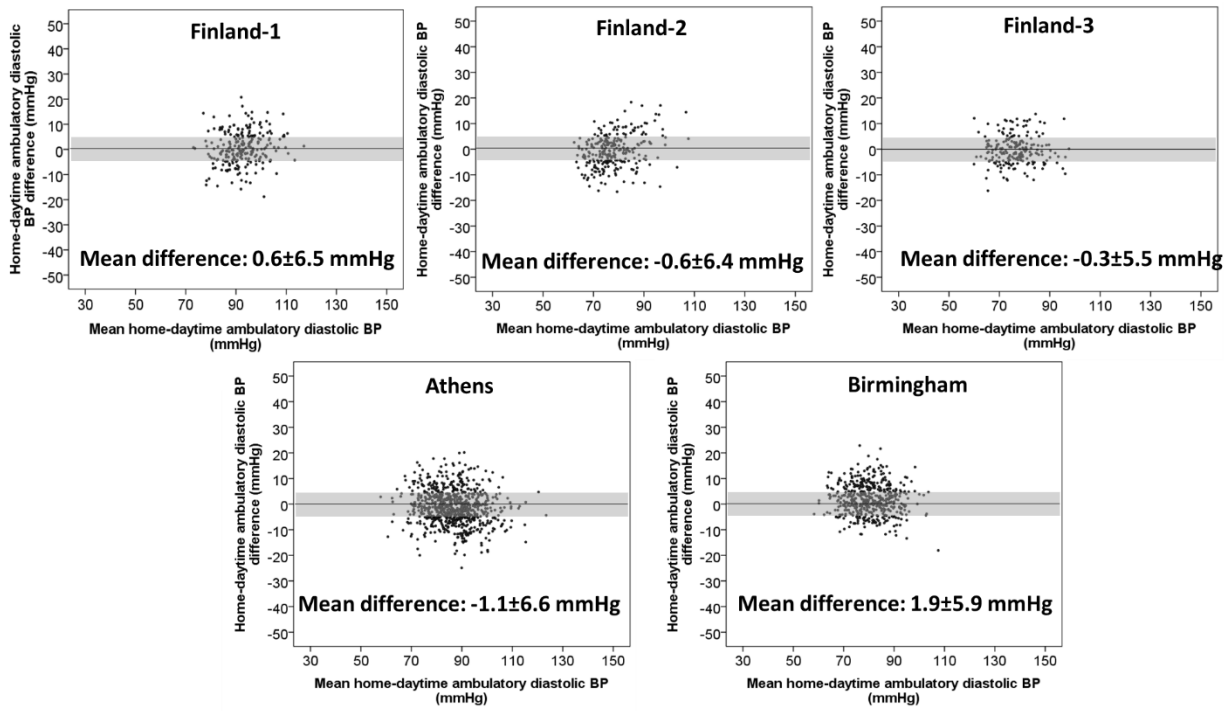
Supplementary Figure 1.

Modified Bland-Altman scatterplots for home versus daytime ambulatory systolic blood pressure (BP) difference for each of the 5 centers included in the analysis (shaded area represents *diagnostically uncertain* differences ≤10 mmHg).



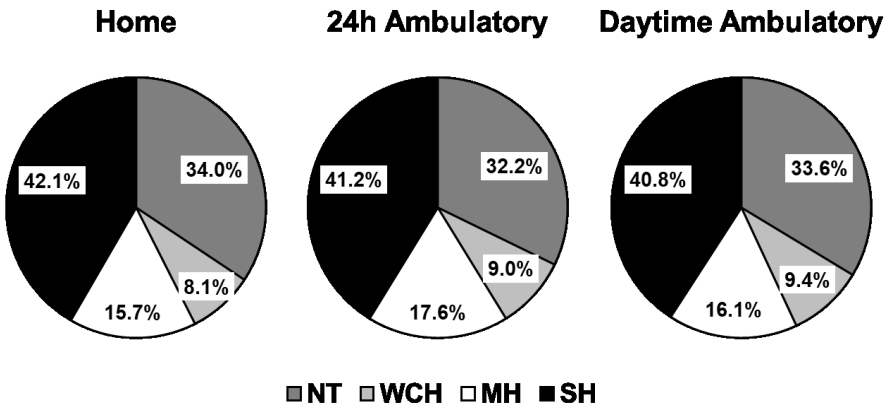
Supplementary Figure 2.

Bland-Altman Plots for home versus daytime ambulatory diastolic blood pressure (BP) difference for each of the 5 centers included in the analysis (shaded area represents *diagnostically uncertain* differences ≤5 mmHg).



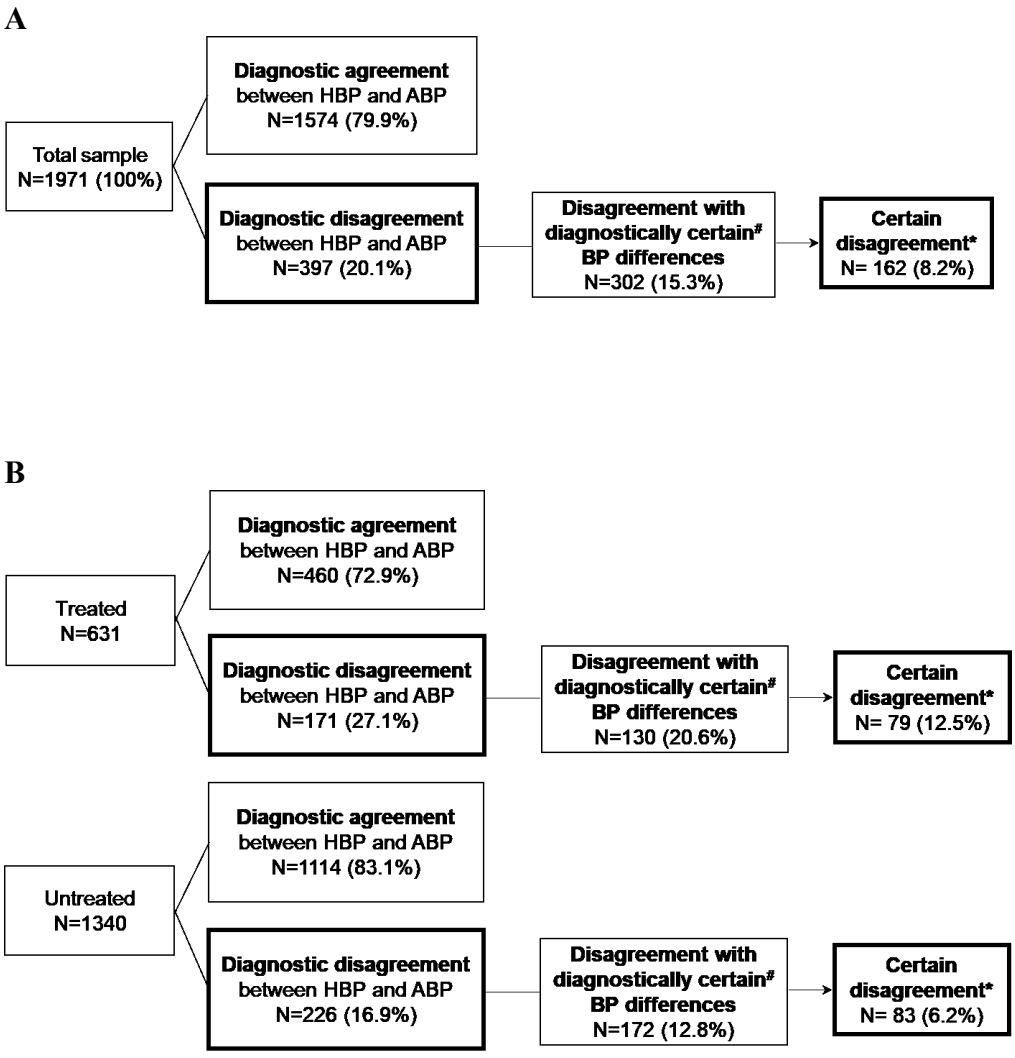
Supplementary Figure 3.

Proportion of subjects with normotension or controlled hypertension (NT), white-coat or white-coat uncontrolled hypertension (WCH), masked or masked uncontrolled hypertension (MH) and sustained hypertension or uncontrolled hypertension (SH) diagnosed using home or ambulatory blood pressure monitoring.



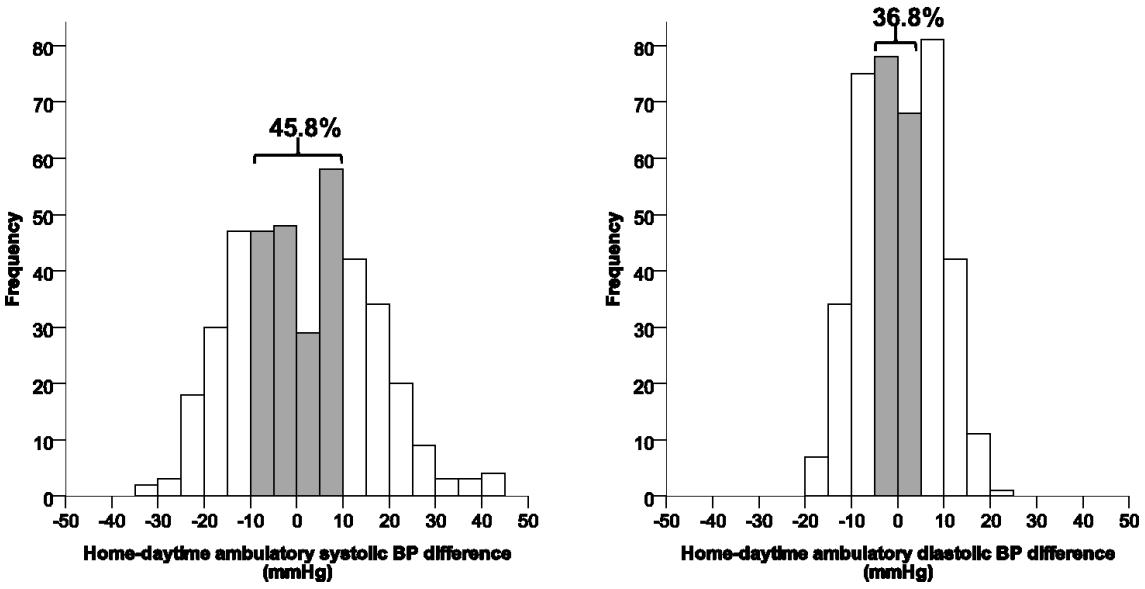
Supplementary Figure 4.

Flowcharts for calculation of *certain* diagnostic disagreement between home (HBP) and daytime ambulatory BP (ABP) in **A)** total sample and **B)** treated and untreated subjects. #, absolute systolic/diastolic HBP-ABP differences >10/5 mmHg; *, excluding cases with HBP and/or ABP differing ≤5 mmHg from the respective diagnostic threshold.



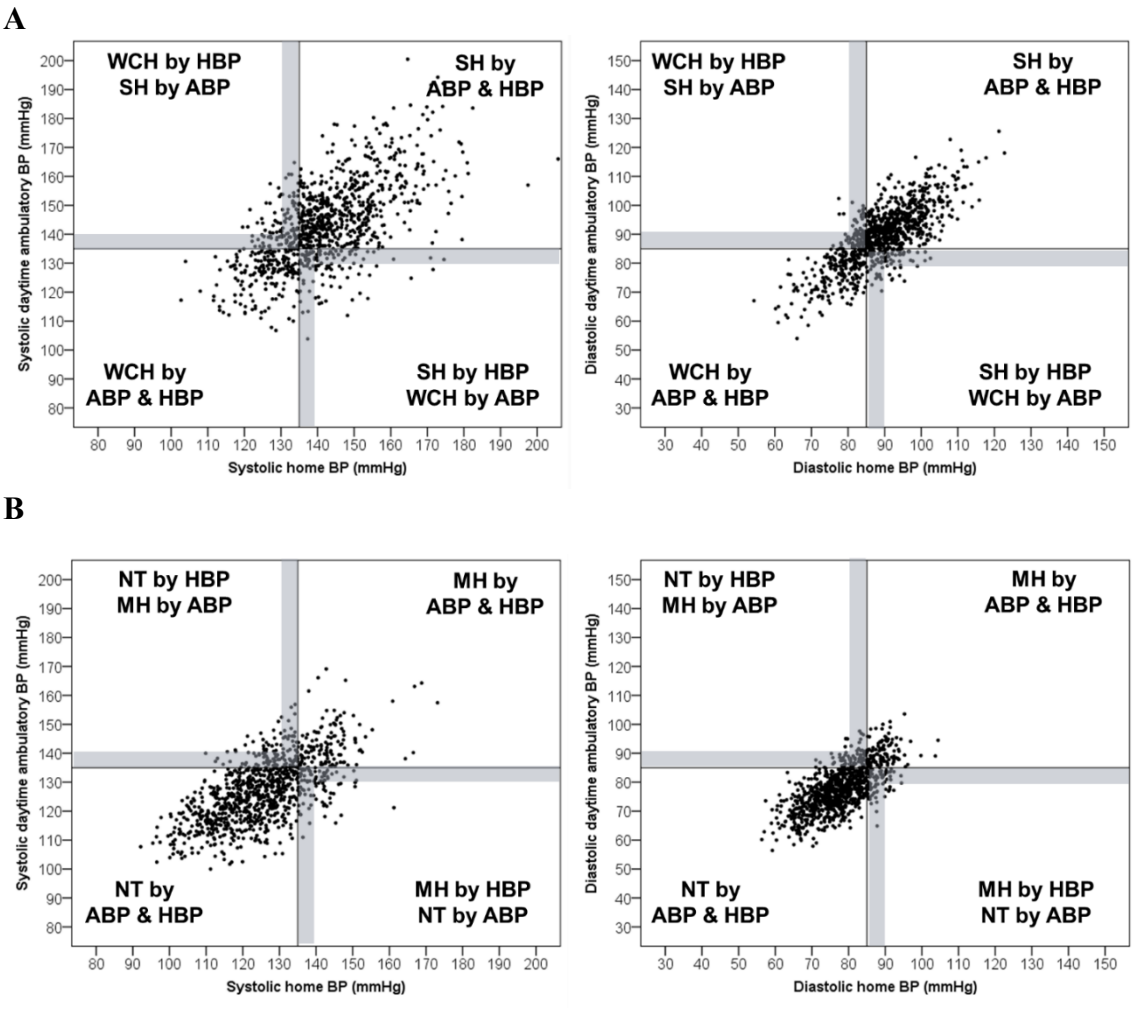
Supplementary Figure 5.

Distribution of blood pressure (BP) differences between home and daytime ambulatory BP in 397 participants with diagnostic disagreement (shaded area represents *diagnostically uncertain* systolic/diastolic differences within 10/5 mmHg).



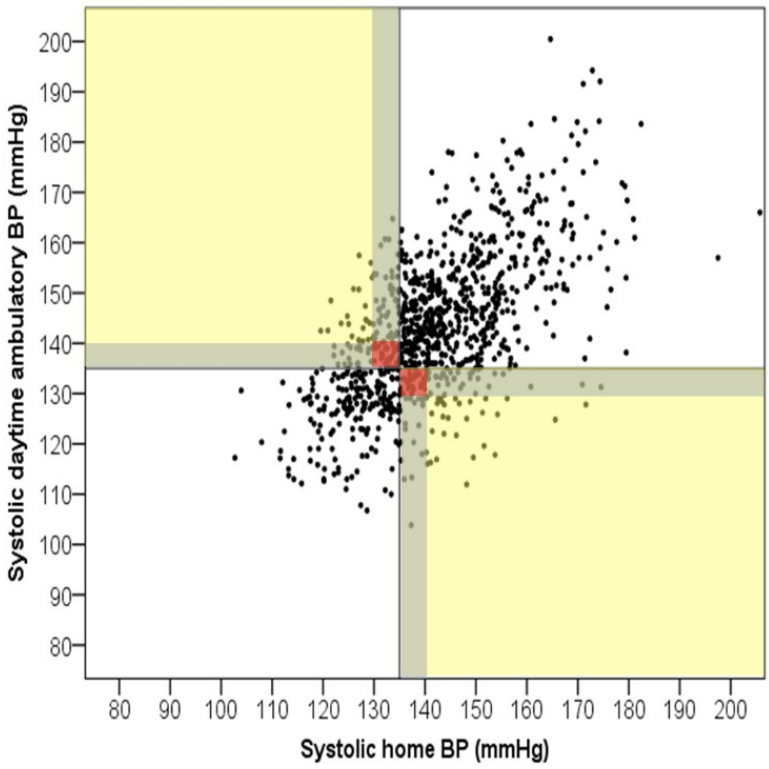
Supplementary Figure 6.

Disagreement between daytime ambulatory (ABP) and home (HBP) BP monitoring in the diagnosis of BP phenotypes in participants (**A**, upper panel) with office hypertension (systolic and/or diastolic) and (**B**, lower panel) office normotension (systolic and diastolic). Grey-shaded area represents a 5-mmHg zone of uncertain diagnosis close to the diagnostic threshold for home and ambulatory hypertension. NT, normotension (for untreated subjects or controlled hypertension for treated); MH, masked hypertension (for untreated subjects or masked uncontrolled hypertension for treated); WCH, white-coat hypertension (for untreated subjects or white-coat uncontrolled hypertension for treated); SH, sustained hypertension (for untreated or uncontrolled hypertension for treated).



Supplementary Figure 7.

Illustration of *certain* diagnostic disagreement between systolic home (HBP) and daytime ambulatory (ABP) levels in subjects with office hypertension. Red areas: disagreement with *diagnostically uncertain* systolic BP difference (absolute value ≤10 mmHg). For example, HBP 136 mmHg with daytime ABP 134 mmHg. Grey zones: disagreement with HBP and/or ABP differing ≤5 mmHg from the respective diagnostic threshold. For example, daytime ABP 115 mmHg and HBP 137 mmHg. Yellow quarters: *certain* diagnostic disagreement.



Supplementary Table 1.

Comparison of participants' characteristics among 5 cohorts (*, p<0.001).

Characteristics	Finland-1	Finland-2	Finland-3	Birmingham	Athens
N	235	261	202	488	785
Males (%)*	140 (59.6)	128 (49)	87 (43.1)	233 (52.3)	449 (57.2)
Ethnicity (%)*					
- Caucasian	235 (100)	261 (100)	202 (100)	233 (47.7)	785 (100)
- African Caribbean	0 (0)	0 (0)	0 (0)	138 (28.3)	0 (0)
- South Asian	0 (0)	0 (0)	0 (0)	117 (24)	0 (0)
Age (years)*	46.1±4.8	49.6±8.4	60±12.6	59.5±9.3	52.4±12.1
(range)	(35-54)	(34-64)	(32-80)	(40-75)	(18-86)
Body mass index (kg/m^2)*	27.9±4.4	26.6±4.7	27±4.9	29.9±6.8	28.5±4.4
Waist circumference (cm)*	93.8±12.6	88.9±13.7	93±14.3	98.4±14.5	103.7±13
Current smoking (%)*	60 (25.5)	72 (27.6)	16 (7.9)	68 (13.9)	179 (27.2)
Alcohol consumption (gr/week)*	105±126.9	80.4±120.1	67±108.8	28.7±48.8	35.6±74.79
Cardiovascular disease (%)*	0 (0)	16 (6.1)	14 (6.9)	68 (13.9)	25 (3.6)
Antihypertensive treatment (%)	3 (1.3)	35 (13.4)	60 (29.7)	313 (64.1)	220 (25)
Diabetes mellitus (%)*	8 (3.4)	8 (3.1)	26 (12.9)	73 (15)	30 (4.4)
Hypercholesterolemia (%)*	153 (65.1)	159 (60.9)	103 (51)	170 (34.8)	375 (54.5)
Office hypertension (%)*	193 (82.1)	41 (15.7)	34 (16.8)	151 (30.9)	571 (72.7)
Home hypertension (%)*	195 (83)	61 (23.4)	63 (31.2)	265 (54.3)	556 (70.8)
Ambulatory hypertension (daytime) (%)*	214 (91.1)	81 (31)	64 (31.7)	219 (44.9)	545 (69.4)

Supplementary Table 2.

Diagnosis of hypertension phenotypes (systolic and/or diastolic) using daytime ambulatory or home blood pressure monitoring (diagnostic agreement 79.9%, kappa 0.70; diagnostic disagreement 20.1% in boxes).

		Daytime Ambulatory Blood Pressure				
		NT	WCH	MH	SH	Total
Home Blood Pressure	NT	551	0	120	0	671 (34%)
	WCH	0	90	0	70	160 (8.1%)
	MH	112	0	198	0	310 (15.7%)
	SH	0	95	0	735	830 (42.1%)
Total		663 (33.6%)	185 (9.4%)	318 (16.1%)	805 (40.8%)	1971 (100%)

NT, normotension in untreated subjects or controlled hypertension in treated; WCH, white-coat hypertension in untreated or white-coat uncontrolled hypertension in treated ; MH, masked hypertension in untreated and masked uncontrolled hypertension in treated; SH, sustained hypertension in untreated or uncontrolled hypertension in treated.

Supplementary Table 3.

Disagreement between daytime ambulatory (ABP) and home blood pressure (HBP) in the diagnosis of hypertension phenotypes among 981 participants with office normotension and among 990 participants with office hypertension (systolic and/or diastolic).

	Diagnostic Agreement		**Diagnostic Disagreement**		**Agreement (kappa)**	**Overall disagreement**	*** Certain disagreement**
Low OBP N=981	NT by ABP + HBP	MH by ABP + HBP	NT by ABP MH by HBP	NT by HBP MH by ABP	76.4% (0.46)	23.6%	9.1%
	551 (56.2%)	198 (20.2%)	112 (11.4%)	120 (12.2%)			
High OBP N=990	SH by ABP + HBP	WCH by ABP + HBP	SH by ABP WCH by HBP	SH by HBP WCH by ABP	83.3% (0.42)	16.7%	7.4%
	735 (74.6%)	90 (9.1%)	70 (7.1%)	95 (9.6%)			
Total					79.9% (0.70)	20.1%	8.2%

OBP, office blood pressure; NT, normotension in untreated or controlled hypertension in treated; WCH, white-coat hypertension in untreated or white-coat uncontrolled hypertension in treated; MH, masked hypertension in untreated and masked uncontrolled hypertension in treated; SH, sustained hypertension in untreated or uncontrolled hypertension in treated. *, excluding cases with HBP and/or ABP differing ≤5 mmHg from the respective diagnostic threshold.

Supplementary Table 4.

Sensitivity analyses for home (HBP) versus ambulatory blood pressure (ABP) differences among participants' subgroups.

BP difference	**HBP - 24-hour ABP**	**HBP - Daytime ABP**
Antihypertensive treatment		
Treated	6.6±10.2/4.7±6.0	2.6±10.6/1.5±6.4
Untreated	1.7±10.3*/3.4±5.9*	-3.3±10.5*/-0.7±6.3*
Office BP		
High	4.2±11.5/4.5±6.3	-1.1±11.9/0.1±6.8
Low	2.4±9.3*/3.1±5.6*	-1.8±9.7/-0.1±6.0
Age (years)		
≤30	3.8±8.8/5.3±6.9	-3.0±9.9/-1.3±7.4
30-60	1.2±9.9/3.4±6.0	-3.8±10.1/-0.7±6.4
≥60	7.5±10.6*/4.6±5.8*	3.5±10.8#/1.5±6.1#

*, $p<0.001$ for difference from 1st subgroup (untreated versus treated; low versus high office BP; age ≥60 versus 30-60 years); #, $p<0.001$ for difference from the other two age subgroups.

Supplementary Table 5.

Linear regression models for determinants of the difference between home (HBP) and daytime ambulatory systolic blood pressure. Sensitivity analyses performed by excluding one study at a time.

	All included	**Cohort excluded**				
		Finland-1	Finland-2	Finland-3	Athens	Birmingham
R^2	0.26	0.26	0.23	0.27	0.33	0.28
Determinants		β coefficients				
Age (years)	0.20*	0.20*	0.21*	0.17*	0.21*	0.22*
Female gender	0.03	-0.14	-0.02	0.26	0.17	-0.08
Antihypertensive treatment	1.04	1.12	0.53	1.30*	2.34*	0.08
Ethnicity (vs Caucasians)						
- African Caribbean	1.01	1.03	1.10	0.80	0.81	-
- South Asians	1.58	1.50	1.49	1.42	1.63	-
Center		(vs Birmingham)				(vs Athens)
- Finland-1	-8.07*	-	-8.08*	-8.52*	-7.00*	-9.21*
- Finland-2	-5.49*	-5.54*	-	-5.79*	-5.20*	-6.41*
- Finland-3	-1.94	-1.94	-1.99	-	-2.23	-3.23*
- Athens	1.29	1.20	1.20	1.01	-	-
Body mass index (kg/m^2)	0.21*	0.17*	0.21*	0.21*	0.22*	0.23*
Cardiovascular disease	2.09*	2.06*	2.53*	2.03	0.51	3.87*
Diabetes	0.78	1.02	1.00	1.37	-0.16	0.33
Hypercholesterolemia	-0.04	-0.04	0.16	0.10	0.04	-0.53
Smoking	0.24	0.32	0.04	0.40	-0.03	0.23
Alcohol (per 10 gr/week)	-0.02	-0.02	-0.04	0.002	0.01	-0.02
Office hypertension	1.32*	1.48*	1.48*	1.41*	0.14	1.76*
Number of HBP readings	-0.08	-0.08	-0.09	-0.10	-0.11	-0.10

Results adjusted for age, gender, body mass index, ethnicity, cardiovascular disease, diabetes, hypercholesterolemia, smoking status, alcohol consumption, office BP level, antihypertensive drug treatment status, study center and number of home BP readings; *, $p<0.05$).

Supplementary Table 6.

Linear regression models for determinants of the difference between home (HBP) and daytime ambulatory diastolic blood pressure. Sensitivity analyses performed by excluding one study at a time.

	All included	**Cohort excluded**				
		Finland-1	Finland-2	Finland-3	Athens	Birmingham
R^2	0.12	0.12	0.11	0.11	0.16	0.11
Determinants				β coefficients		
Age (years)	0.09*	0.09*	0.08*	0.07*	0.12*	0.12*
Female gender	-0.65*	-0.64	-0.75*	-0.50	-0.97*	-0.34
Antihypertensive treatment	0.82*	0.93*	0.57	0.99*	1.07*	0.61
Ethnicity (vs Caucasians)						
- African Caribbean	0.62	0.67	0.59	0.43	0.57	-
- South Asians	0.86	0.88	0.69	0.72	0.73	-
Center			(vs Birmingham)			(vs Athens)
- Finland-1	1.07	-	0.82	0.66	1.58*	2.66*
- Finland-2	0.31	0.22	-	0.08	0.79	2.00*
- Finland-3	-1.28	-1.20	-1.37	-	-3.23*	0.95
- Athens	-1.75*	-1.55*	-1.92*	-2.03*	-	-
Body mass index (kg/m^2)	0.22*	0.19*	0.20*	0.23*	0.25*	0.26*
Cardiovascular disease	1.21	1.21	1.13	1.26	0.58	1.86*
Diabetes	0.43	0.51	0.43	0.85	-0.04	0.17
Hypercholesterolemia	-0.02	-0.10	0.26	0.05	0.12	-0.49
Smoking	-0.04	0.01	-0.13	0.10	-0.21	-0.16
Alcohol (per 10 gr/week)	-0.01	0.004	-0.03	0.004	-0.001	-0.01
Office hypertension	1.05*	0.80*	0.86*	1.18*	1.01*	1.35*
Number of HBP readings	-0.05	-0.03	-0.04	-0.05	-0.20*	0.02

Results adjusted for age, gender, body mass index, ethnicity, cardiovascular disease, diabetes, hypercholesterolemia, smoking status, alcohol consumption, office BP level, antihypertensive drug treatment status, study center and number of home BP readings; *, $p<0.05$